

## Iloperidone (Fanapt): An FDA-Approved Treatment Option for Schizophrenia

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### INTRODUCTION

Schizophrenia is a debilitating and chronic mental illness that affects approximately 24 million people of all ages around the world. The usual onset is between 15 and 35 years of age,<sup>1</sup> and about 1% of all Americans are affected.<sup>2</sup> Approximately 25% of all beds in psychiatric hospitals are occupied by patients with schizophrenia, and 50% of psychiatric hospital admissions are a result of schizophrenia.<sup>3,4</sup> This mental illness can be characterized by the presentation of psychosis, cognitive impairment, social withdrawal, and apathy, all of which lead to impaired functioning in school, self-care, recreational activities, work, parenting, and interpersonal relationships. Among the psychiatric disorders, schizophrenia is considered to be the most disabling illness.<sup>5</sup> Symptoms can broadly be classified into three groups:

- *positive*: unusual perceptions or thoughts such as hallucinations and delusions
- *negative*: a decrease or loss in the ability to speak, to find pleasure in everyday life, to express emotions, or to initiate plans. These symptoms are often mistaken for depression or amotivation; hence they are more difficult to recognize.
- *cognitive*: difficulty in organizing or planning, with impairments in executive functioning, working memory, and attention. These are considered the most disabling of the symptoms because they affect the patient's ability to maintain a normal life.<sup>6</sup>

Two general classes of medications are used to treat schizophrenia: first-generation (conventional) antipsychotic agents and second-generation (atypical) antipsychotic agents.

The most commonly used first-generation antipsychotic drugs are chlorpromazine (Thorazine, GlaxoSmithKline), haloperidol (Haldol, Ortho-McNeil), perphenazine (Trilafon, Schering), and fluphenazine (Prolixin, Apothecon). Although efficacious, these medications are associated with a high risk of causing extrapyramidal symptoms, including rigidity, tremors, dystonia, and restlessness.

In 1990, the first of the atypical agents, clozapine (Clozaril, Novartis), was approved in the U.S. Although clozapine is considered to have extrapyramidal symptoms as a rare side effect, it carries five black box warnings, the most serious being agranulocytosis. Many other atypical agents are known for their metabolic side effects such as weight gain and an increased risk of hyperglycemia and hyperlipidemia. Other atypical antipsychotic medications include risperidone (Risperdal, Janssen), olanzapine (Zyprexa, Eli Lilly), quetiapine (Seroquel, AstraZeneca), ziprasidone (Geodon, Pfizer), aripiprazole (Abilify, Bristol-Myers Squibb/Otsuka), paliperidone (Invega, Janssen), and asenapine (Saphris, Schering-Plough).<sup>6</sup>

In May 2009, the FDA approved iloperidone (Fanapt, Vanda) as an atypical antipsychotic agent for the acute treatment of patients with schizophrenia. In clinical trials, it was shown to be efficacious and safe. In this article, we review the pharmacology, pharmacokinetics, safety, and efficacy of iloperidone in alleviating both the positive and negative symptoms of this disabling disease.

## INDICATION AND USAGE<sup>7</sup>

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Iloperidone is indicated for the acute treatment of schizophrenia in adults of at least 18 years of age.

## CHEMICAL AND PHYSICAL PROPERTIES<sup>7</sup>

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A psychotropic agent, iloperidone belongs to the piperidinyl-benzisoxazole class. In the form of a finely crystalline, white to off-white powder, it is practically insoluble in water, only slightly soluble in 0.1N hydrochloric acid, and freely soluble in chloroform, ethanol, methanol, and acetonitrile. It is available as an uncoated tablet in dosages of 1, 2, 4, 6, 8, 10, and 12 mg.

## CLINICAL PHARMACOLOGY

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### Mechanism of Action

The exact mechanism by which iloperidone has efficacy in treating schizophrenia is unknown; however, it is suggested that its efficacy is mediated via a combination of serotonin type-2 (5-HT<sub>2</sub>) and dopamine type-2 (D<sub>2</sub>) antagonism.<sup>7</sup>

### Pharmacokinetics

**Absorption and Distribution** According to the manufacturer, iloperidone tablets are absorbed within two to four hours after they are taken. A possible advantage of iloperidone is its oral bioavailability (96%) without regard to food intake (Table 1).<sup>8</sup> Administering iloperidone with high-fat meals does not significantly affect the peak concentration (C<sub>max</sub>) or the area under the curve (AUC) of iloperidone and its metabolites (P88 or P95), but the time to peak concentration (T<sub>max</sub>) is delayed by one hour for iloperidone, two hours for P88, and six hours for P95. Iloperidone and its metabolites are approximately 95% bound to serum proteins.

**Table 1**

Pharmacokinetic Properties of Iloperidone (Fanapt) and Its Metabolites

	Iloperidone	P88	P95
<b>Absorption and distribution</b>			
Oral bioavailability	96%		
Protein binding	95%		
T <sub>max</sub>	1 hour	2 hours	6 hours
AUC			
Extensive metabolizers		19.5%	47.9%
Poor metabolizers		34%	25%
<b>Metabolism and elimination</b>			
Half-life			
Extensive metabolizers	18 hours	26 hours	23 hours
Poor metabolizers	33 hours	37 hours	31 hours
Metabolic pathway	Carbonyl reduction, CYP 2D6 Hydroxylation, CYP 2D6 O-demethylation, CYP 3A4		
Excretion	Renal, 50% Fecal, 20%		

AUC = area under the curve; CYP = cytochrome P450; T<sub>max</sub> = time to peak concentration.

Data from Fanapt (iloperidone) product information;<sup>8</sup> Weiden PJ, et al. *J Clin Psychopharmacol* 2008;25:S12–S19;<sup>9</sup> Potkin SG, et al. *J Clin Psychopharmacol* 2008;28:S4–S11;<sup>11</sup> and Kane JM, et al. *J Clin Psychopharmacol* 2008;28:S29–S35;<sup>12</sup>

**Metabolism and Elimination** Iloperidone is metabolized by carbonyl reduction, hydroxylation (mediated by cytochrome P450 2D6), and O-demethylation (mediated by cytochrome P450 3A4). There are two predominant metabolites:

- P95 represents 47.9% of the AUC for extensive metabolizers and 25% for poor metabolizers.
- P88 accounts for 19.5% of the AUC in extensive metabolizers and 34% of the AUC in poor metabolizers.

Extra monitoring and dose adjustments are necessary when iloperidone is given with an inhibitor of CYP 2D6 or CYP 3A4.

The elimination half-lives of iloperidone, P88, and P95 are 18, 26, and 23 hours, respectively, in extensive metabolizers and 33, 37, and 31 hours in poor metabolizers, respectively. Steady-state concentrations are attained within three to four days of dosing. Approximately 50% of the product is excreted in the urine, and 20% is eliminated via the feces.

## CLINICAL EFFICACY

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Weiden et al.<sup>9</sup>

Weiden and associates pooled together an analysis of three previously completed trials between October 1998 and June 2002. The trials formed the basis for the phase 3 studies reported by Cutler et al.<sup>10</sup> because the results of these earlier trials were yet to be published. All three trials involved double-blind treatment and long-term extension phases, but only six-week results were considered for this analysis.

After a single-blind, placebo run-in period of three days, patients who met the inclusion criteria were randomly assigned to the studies.

For study 1, they received iloperidone 4 mg, 8 mg, or 12 mg/day, haloperidol 15 mg/day, or placebo.

For study 2, they received iloperidone 4 to 8 mg/day, iloperidone 10 to 16 mg/day, iloperidone 20 to 24 mg/day, risperidone 4 to 8 mg/day, or placebo.

For study 3, patients received iloperidone 12 to 16 mg/day, iloperidone 20 to 24 mg/day, risperidone 6 to 8 mg/day, or placebo.

To be eligible for enrollment into these studies, subjects had to:

- be between the ages of 18 and 65.
- have a diagnosis of acute or subacute exacerbation of schizophrenia or schizoaffective disorder in need of treatment.
- have a Positive and Negative Syndrome Scale (PANSS) score above 60 at baseline.

Subjects were excluded if they:

- had received clozapine within 60 days prior to trial admission.
- had required continuous treatment with other psychotropic drugs, including antidepressants and mood stabilizers.
- had not improved after sufficient exposure to any antipsychotic treatment in the previous two years.

When the studies were combined, 1,943 patients were randomly assigned to receive iloperidone 4 to 8 mg (n = 399), iloperidone 10 to 16 mg (n = 522), iloperidone 20 to 24 mg (n = 145), haloperidol 15 mg (n = 124), risperidone 4 to 8 mg (n = 310), or placebo (n = 443) daily. Baseline patient demographics were similar in all studies. The primary objective in the three studies was to determine the efficacy of iloperidone compared with placebo. The primary endpoint in study 1 was the PANSS total score (PANSS-T); from baseline, there was a significant improvement with iloperidone 12 mg/day ( $P = 0.047$ ) and haloperidol ( $P < 0.001$ ).

In studies 2 and 3, Brief Psychiatric Rating Scale scores (BPRS) were the primary variable for efficacy. Scores improved with risperidone and iloperidone when compared with placebo, with iloperidone 4 to 8 mg/day ( $P = 0.012$ ), and with iloperidone 10 to 16 mg/day ( $P = 0.001$ ). In study 3, iloperidone 20 to 24 mg/day ( $P = 0.010$ ), was superior. The risperidone  $P$  value was not disclosed. In study 3, there was no improvement in BPRS scores with iloperidone 12 to 16 mg/day.

The results of all secondary endpoints assessed were based on last observation carried forward (LOCF).

In study 1, iloperidone 12 mg/day was significantly more effective than placebo in improving BPRS scores. In study 2:

- With iloperidone 4 to 8 mg/day, PANSS-T scores, PANSS-Positive subscale (PANSS-P) scores, PANSS-General Psychopathology subscale (PANSS-GP) scores, and Clinical Global Impression of Severity (CGI-S) scores were significantly improved.
- With iloperidone 10 to 16 mg/day, PANSS-T, PANSS-P, PANSS-GP, and CGI-S scores were decreased.
- With iloperidone 20 to 24 mg/day, PANSS-T, PANSS-P, Negative sub-scale (PANSS-N), PANSS-GP, and CGI-S scores were significantly decreased.

#### Potkin et al.<sup>11</sup>

Of the 1,943 randomized patients, 1,912 received at least one dose of the study medication and were analyzed for the safety profile. This included 440 patients taking placebo, 463 patients receiving iloperidone 4 to 8 mg/day, 456 patients receiving iloperidone 10 to 16 mg/day, 125 patients receiving iloperidone 20 to 24 mg/day, 118 patients receiving haloperidol 15 mg/day, and 306 patients receiving risperidone 4 to 8 mg/day. The most common treatment-related ADEs noted with iloperidone were dizziness, dyspepsia, dry mouth, and somnolence. Haloperidol subjects displayed extrapyramidal disorders, dystonia, akathisia, and tremors. Risperidone subjects experienced extrapyramidal disorders, somnolence, tremor, and akathisia.

The most common treatment-related ADEs leading to discontinuation were dizziness, psychiatric disorders, and nausea with iloperidone; tremor, psychiatric disorders, nausea, and dizziness with haloperidol; and somnolence, dizziness, and extrapyramidal symptoms with risperidone.

In each study at all doses with iloperidone, there was significant improvement in the overall rating of extra-pyramidal symptoms according to the Extrapyramidal Symptom Rating Scale (ESRS). Patients with akathisia, including restlessness, an inability to keep still, and nervousness, showed significant improvement from baseline with iloperidone 10 to 16 mg and 20 to 24 mg compared with placebo. In all dosage ranges for iloperidone, a decrease in blood pressure was noted, but only for the first week of treatment; generally, the reduction was not sustained.

Orthostasis occurred less often with iloperidone doses of 20 to 24 mg/day compared with doses of 10 to 16 mg/day; however, this ADE was observed more frequently with all doses of iloperidone than with placebo. Significance was found in the QT interval in all dose ranges of iloperidone and a mean weight gain of 2.4 kg in all iloperidone patients. Blood glucose changes were similar for all treatment groups, total cholesterol changes were not significant in any group, and triglycerides and prolactin levels were generally decreased with all dosages of iloperidone.

#### Kane et al.<sup>12</sup>

This trial consisted of three prospective, multicenter, double-blind, flexible-dose, parallel-group studies from 121 centers worldwide. It was conducted to evaluate and analyze the long-term efficacy and safety of iloperidone (range, 4–16 mg/day) compared with haloperidol (range, 5–20 mg/day). To be eligible, subjects had to:

- be between 18 and 65 years of age.
- have a diagnosis of schizophrenia or schizoaffective disorder, as defined in the *Diagnostic Statistical Manual of Mental Disorders*, 4th edition (DSM-IV).

- have a PANSS-T score above 60.
- have normal vital signs.
- have no contraindications to any study medication.
- have the availability of a caregiver to ensure and support treatment adherence.
- have a negative pregnancy test and had to be using contraception if they were of childbearing age.

Patients had a one-day to two-day run-in period before receiving iloperidone 2 to 8 mg/day or haloperidol 10 mg/day. Doses were titrated during the initial six-week, double-blind phase, and patients who completed this earlier phase were eligible to continue into a 46-week, long-term, double-blind maintenance phase. The study randomized 1,644 patients into the initial six-week phase (1,239 receiving iloperidone and 405 receiving haloperidol). Of these patients, 36.6% (371) in the iloperidone group and 37.8% (118) in the haloperidol group showed a treatment response and were eligible to continue on to the 46-week maintenance phase. Baseline demographics were similar in both groups.

During the maintenance phase, 36.4% of the haloperidol patients and 36.4% of the iloperidone patients discontinued treatment. The most common reasons were withdrawal of consent and an unsatisfactory therapeutic effect. Serious ADEs were reported in 18.1% of patients in the iloperidone group and 16.1% in the haloperidol group; the most common reasons for discontinuation were psychiatric disorders in the iloperidone group and nervous system disorders in the haloperidol group. The most common serious ADEs reported were exacerbations of psychosis and of schizophrenia in both groups.

The primary variable for efficacy was time to relapse, which was defined as an increase (worsening) in the PANSS-T score by 25% or more, including a change of 10 points or greater; discontinuation because of lack of efficacy; aggravated psychosis with hospitalization; or a two-point or greater increase in Clinical Global Impression of Change (CGI-C) scores after six weeks.

Patients receiving iloperidone and haloperidol had similar rates of relapse (43.4% and 41.2%, respectively). Reasons for relapse were also similar: increased PANSS scores in 25.9% of the iloperidone group and increased scores in 29.8% of the haloperidol group, worsened psychosis with hospitalization in 7.5% of the iloperidone group and in 6.1% of the haloperidol group, and an increase in CGI-C scores in 10% of the iloperidone group and in 5.3% of the haloperidol group. The mean number of days prior to relapse was 89.9 days for the iloperidone patients and 101.8 days for the haloperidol patients; 65% of iloperidone patients showed improved CGI-C scores, compared with 66% of haloperidol patients.

In summary, iloperidone was considered to be safe and well tolerated and as effective as haloperidol in preventing relapse during long-term treatment.

## ADVERSE DRUG EFFECTS

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On the basis of two published clinical trials (see Clinical Efficacy in Weiden and Kane),<sup>9,12</sup> the most commonly reported adverse drug event (ADE) was dizziness in approximately 12.1% of patients taking iloperidone 4 to 8 mg/day, in 10.3% of those taking 10 to 16 mg/day, and in 23.2% of those given 20 to 24 mg/day, compared with 6.8% of those receiving placebo.<sup>8</sup> In the second study, insomnia was the major ADE, affecting between 18.1% and 21.1% of patients receiving a mean iloperidone dose of 11.8 mg/day, compared with 25.1% of patients receiving a mean haloperidol dose of 13.2 mg/day.<sup>9</sup> Somnolence, dry mouth, and dyspepsia were also reported at all dosage ranges, but extrapyramidal symptoms were reported with the same frequency as placebo in both trials.

The dosage range of iloperidone with the lowest rate of ADEs is between 10 and 16 mg/day. The highest incidence of ADEs was in patients taking 20 to 24 mg/day. ADEs occurring in at least 5% of patients were akathisia, dizziness, dry mouth, dyspepsia, dystonia, fatigue, somnolence, extrapyramidal disorders, nasal congestion, and tremors. Akathisia, dizziness, flatulence, and tremor were noted at the lowest rates in patients receiving iloperidone 10 to 16 mg. Dyspepsia and dystonia, however, were observed with the lowest frequency in the iloperidone 20- to 24-mg group.<sup>9</sup>

The incidence of corrected QT (QTc) prolongation with iloperidone was equal to that observed with ziprasidone. The mean increase was 7.2 msec with iloperidone and 6.1 msec with ziprasidone in the study by Cutler et al.<sup>11</sup>

## DRUG INTERACTIONS<sup>7</sup>

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Because iloperidone is metabolized via CYP 2D6 and 3A4, caution is advised when it is given together with strong CYP inhibitors. The iloperidone dose should be reduced by half when it is coadministered with these strong CYP inhibitors. Given that iloperidone displays primarily CNS effects, alcohol and other centrally acting drugs should be used with caution. In addition, considering the  $\alpha_1$  antagonism characteristics of iloperidone, the effect of anti-hypertensive agents would be potentiated when administered concomitantly.

## CONTRAINDICATIONS<sup>7</sup>

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There are no contraindications to the use of iloperidone other than a known hypersensitivity to the product or any of the components in the formulation. Pruritus and urticaria have been reported as symptoms of hypersensitivity.

## WARNINGS<sup>7</sup>

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There is an antipsychotic class-related boxed warning for the risk of increased mortality in elderly patients with dementia-related psychosis. Iloperidone is not indicated for these patients. Other warnings address a prolonged QT interval (cardiovascular events), neuroleptic malignant syndrome, tardive dyskinesia, hyperglycemia and diabetes, seizures, weight gain, orthostatic hypotension and syncope, leukopenia, neutropenia, dysphagia, agranulocytosis, hyperprolactinemia, body temperature dysregulation, suicide risk, priapism, and the potential for cognitive and motor impairment.

## DOSAGE AND ADMINISTRATION<sup>7</sup>

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**Adults.** The recommended starting dose is 1 mg twice daily and should be increased to reach the target dosage range of 6 to 12 mg twice daily by increasing the daily dose to 2 mg twice daily on day 2, 4 mg twice daily on day 3, 6 mg twice daily on day 4, 8 mg twice daily on day 5, 10 mg twice daily on day 6, and 12 mg twice daily on day 7. The drug must be titrated from a low starting dose to avoid the orthostatic hypotension resulting from its  $\alpha$ -adrenergic blocking properties. The maximum recommended dose is 12 mg twice daily (24 mg/day).

**Pregnant and lactating patients.** Iloperidone is categorized as a Pregnancy Category C drug. No studies have been conducted with iloperidone in pregnant women or nursing mothers. It is not known whether the drug or any of its metabolites are excreted in human milk. Women receiving iloperidone are advised not to breast-feed. The potential risks and benefits of using iloperidone in this population should be considered.

**Pediatric populations.** The safety and efficacy in pediatric and adolescent patients have not been established.



**Hepatically impaired patients.** Iloperidone is not recommended for patients with hepatic impairment.

**Renally impaired patients.** No dose adjustment is suggested for patients with renal impairment.

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## ACQUISITION COST

At the time of this writing, pricing information was not yet available from the manufacturer or from wholesalers.

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## CONCLUSION

When considering the 20 or so antipsychotic agents on the market for the treatment of schizophrenia, health care professionals should consider a variety of factors, including the findings of iloperidone's warning for causing QTc prolongation. Consequently, other medications should be considered as first-line therapy. When prescribers are deciding whether to place iloperidone on the formulary in a health care organization, they should also compare its relative efficacy, adverse-effect profile, cost, any patient-specific variables (e.g., drug–drug interactions, genetic polymorphisms), and metabolic properties with other anti-psychotic medications currently available.

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## Footnotes

**Disclosure:** The authors have no financial or commercial relationships to report in regard to this article.

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